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Clustering of Hypertension, Diabetes, and Obesity in Adult Male Twins: Same Genes or Same Environments?

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Summary

We investigated the mediating role of genetic factors in the clustering of hypertension, diabetes, and obesity, using the twin registry maintained by the National Academy of Sciences—National Research Council. The study sample included 2,508 male twin pairs born between 1917 and 1927 who responded to a mailed questionnaire that covered demographic variables, cardiovascular risk factors, and health behaviors. The incidence of hypertension and diabetes in this cohort was ascertained from subjects' self-report of a physician diagnosis and/or the use of prescription medications. The body-mass index calculated from self-reports of height and weight was used as a measure of obesity. Descriptive analyses indicated probandwise concordance rates of 34.0%, 31.2%, and 32.7%, respectively, for the joint occurrences of hypertension and diabetes, hypertension and obesity, and diabetes and obesity in MZ twin pairs. Corresponding concordance rates in DZ twin pairs were 8.1%, 14.9%, and 2.8%. The probandwise concordance for the clustering of all three conditions in the same individuals was 31.6% in MZ pairs and 6.3% in DZ pairs (relative risk 5.0; $\chi^2(1)=2.6$; $P<.15$). Multivariate genetic modeling of the correlation in liabilities to develop these conditions suggested the presence of a common latent factor mediating the clustering of hypertension, diabetes, and obesity in this twin sample. This common factor was influenced by both genetic and environmental effects (59% genetic, 41% environmental). The genetic influences on the common latent factor were due to dominant rather than additive sources; the environmental influences appeared to be specific rather than shared by co-twins.

Introduction

In recent years, much attention has been paid to findings that hypertension, hyperlipidemia, and diabetes mellitus often cluster in the same individuals at a greater frequency than chance alone would predict (Gillum 1987; Mitchel et al. 1990; McKeigue et al. 1991). A metabolic syndrome characterized by the clustering of these cardiovascular risk factors has been suggested by several authors (Williams et al. 1988; Kaplan 1989; Ferrannini et al. 1990). Although the manifestation of this metabolic syndrome is indisputable, the mechanisms involved in its pathogenesis are far from clear. It has been suggested that insulin resistance (Reaven 1988), hyperinsulinemia (Modan et al. 1985), obesity (Bjorntorp 1990), increased sympathetic-nerve activity (Brindley and Rolland 1989), and deranged intracellular handling of ions (Hvarfner et al. 1988) may all have pathogenic importance.

Diabetes, hypertension, and dyslipidemia each have a solid genetic background (Newman et al. 1987; Hunt et al. 1989; Williams et al. 1989), although the precise model of genetic transmission is unknown. Obesity, the more acquired among the clinical manifestations of the metabolic syndrome, seems also to develop from a strong genetic predisposition (Bouchard et al. 1988; Fabsitz et al. 1992). Epidemiology studies have demonstrated a clustering of cardiovascular risk factors in twins and among coronary-prone family members (Hunt et al. 1989; Selby et al. 1991). A formal multivariate analysis, however, of the contribution of genes and the environment to the joint clustering of cardiovascular risk factors among genetic relatives has not been conducted. Studies of twins have been useful as a first step in evaluating the contribution of heredity to complex traits (Martin et al. 1978). More recently, advances in multivariate modeling have paved the way for a better understanding of the causal factors underlying the covariation of multiple traits in twin subjects (e.g., see Neale and Cardon 1992).

In this analysis we used epidemiologic data available on a large sample of male twin subjects to describe twin-pair similarities for the joint clustering of hypertension, diabetes, and obesity in adult life. In addition, we applied to these data recently developed multivariate genetic methods to estimate the contribution of genes and the environment to this metabolic syndrome and its individual components.

Subjects and Methods

Study Subjects

The sample for this study was taken from the National Academy of Sciences–National Research Council (NAS-

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NRC) Twin Registry. The methods used to construct this twin panel have been described elsewhere (Jablon et al. 1967; Hrubec and Neel 1978). In brief, multiple births of white males occurring in the continental United States from 1917 to 1927 were identified by searching birth certificates. Approximately 93% of all such births estimated from national statistics to have occurred during those years were found. These records were linked to the master index file of the Veterans Administration (VAMI), yielding 15,948 pairs of twins in which both had served in the military during World War II.

Zygosity classification was determined from self-reports of twin brothers regarding their degree of similarity or dissimilarity. Later assessments of the accuracy of these reports, based on fingerprints, physical characteristics, and blood typing, estimated the classification to be correct in ~95% of the twin pairs (Cederlof et al. 1961).

An initial epidemiologic questionnaire was mailed to these twins during 1967–69 in a collaborative study with investigators of the Swedish Twin Registry. The English-language questionnaire was essentially a translation of one used in Sweden and later adopted in the Finnish Twin Registry (Cederlof and Lorich 1978; Kaprio et al. 1978). The objective of the survey was to evaluate the prevalence of coronary and respiratory disease and to obtain a history of health practices, including eating habits and tobacco and alcohol consumption. During 1983–85, a follow-up survey was conducted with the same questions asked as were asked at the first survey. In addition, twins were asked whether they had ever been told by a doctor that they had hypertension or high blood pressure and whether they were treated for this condition. A positive response for medication treatment was used to define hypertension in the present study. Similarly, subjects were asked whether they had been told that they have diabetes and how they were treated (insulin injection, pills, and/or diet). A positive response for treatment of any kind was taken as evidence for diabetes. The responses were validated in a subsample of twins participating in the second examination of the National Heart, Lung, and Blood Institute Twin study conducted in 1981–82, where agreement was 82% for hypertension and 87% for diabetes (Carmelli et al. 1994).

There were 9,475 individuals who responded to the 1983–85 NAS-NRC survey (4,292 MZ twins, 4,664 DZ twins, and 519 twins of unknown zygosity). Of the 2,722 complete twin pairs, 1,382 were MZ, 1,221 DZ, and 119 of unknown zygosity. A total of 2,508 pairs with known zygosity and complete data are included in the present analysis. Self-reports of weight and height were used to derive the body-mass index (BMI; kg/m^2) as an overall measure of obesity. Subjects with BMI > 27 were classified as obese.

Statistical Methods

Concordance for the separate and joint occurrences of hypertension, diabetes, and obesity within MZ and DZ twins was estimated in the present study by using the probandwise concordance rate. With complete twin ascertainment, as in the present sample, this concordance assesses the risk of disease among co-twins of affected twins. By this method, the rate is defined as $2C/(2C+D)$, where C is the number of disease-concordant pairs and D is the number of disease-discordant pairs (Smith 1974). The prevalence of disease was calculated as $(2C+D)/2N$, where N is the total number of pairs. A χ^2 analysis that compares the proportion of concordant MZ and DZ pairs among the total number of pairs was used to test the significance of the difference between the MZ and DZ concordance rates.

In addition to the proband concordance rates as measures of twin similarities, we employed another statistic, the tetrachoric correlation, which uses all the information available in the joint and marginal distributions of hypertension, diabetes, and obesity in the present sample. The tetrachoric correlation, or the correlation in liability, assumes that underlying the discrete division of twins into those with and without the disease, there exists a continuous distribution of the liability or vulnerability to disease (Falconer 1965). It is also assumed that a threshold exists on this liability distribution such that individuals with a liability above the threshold will develop the disease while those with a liability below the threshold will remain free of the disease. In principle, this model assumes that each disease in this cluster has a multifactorial etiology involving a large number of genes and environmental factors of small to moderate effect, so that the resulting liability distribution in the sample is approximately normal (Kendler et al. 1992).

In formulating a genetic model for the variation in liability, it is assumed that four parameters, two genetic and two environmental, are contributing factors. Additive genetic variance (A) is the proportion of variance in liability that results from the additive effects of alleles at each locus. Dominance genetic variance (D) is the proportion of total variance that results from nonadditive effects of two alleles at the same locus. The proportions of total variance in liability due to A and A + D are the narrow and broad heritabilities, respectively.

Common environmental variance (C) is that proportion of variance in liability that results from environmental events shared by both members of a twin pair (e.g., rearing environment, age and cohort effects, and social class). Specific environmental variance (E) is that proportion of variance in liability that results from environmental events that are not shared by members of a twin pair and also includes measurement error. Three of the parameters (A, D, and C) contribute to twin similarities; the fourth (E) contributes to twin differences.

In twin studies, the effects of C and D are confounded. As a result, the fits of unconstrained ACE and ADE models are indistinguishable. D and C, however, have opposite

effects on the patterns of intraclass correlations among MZ and DZ twins. Given A, D will increase and C will decrease the ratio of intraclass correlations between MZ and DZ twins. Because parameters in these models are variance estimates, any model that results in a significant negative estimate of C or D will be rejected. For example, negative estimates of C indicate that the ADE model is to be preferred over the ACE model, so that we proceed to obtain estimates of D instead of C.

The objective in the present genetic analysis was to use all the information in the derived tetrachoric correlations of pairwise twin similarities for these conditions in MZ and DZ pairs in order to separate genetic from environmental effects. Specifically, we tested two models that represent different ways in which genes and the environment may affect the correlation. In the first, the "independent-pathway" model (fig. 1, *top*), genes and environment have different and independent effects on the observed correlation. For example, there could be two sets of genes—one selective for the liability to hypertension and one selective for the liability to diabetes—while environmental influences predispose individuals equally to both conditions. In this specific configuration, the environment and not the genetic endowment is responsible for the clustering of hypertension and diabetes. Under the second, "common-pathway" model (fig. 1, *bottom*), both genes and the environment contribute to some unmeasured intermediate (latent) variable, which in turn is responsible for the observed correlation. In this common-pathway model, both genetic and environmental effects, by their influence on the latent variable, can be specific (or nonspecific) in their influence on the liability to hypertension, diabetes, and obesity. The fits of the two models were tested statistically by means of likelihood-ratio χ^2 tests provided by the LISREL program (Joreskog and Sorbom 1989) using weighted least squares (WLS). Tetrachoric correlations and associated asymptotic weight matrices were calculated using the companion program PRELIS (Joreskog and Sorbom 1988).

Another purpose of the model-fitting procedure is to explain the pattern of observed correlations by using as few parameters as possible. To achieve this goal we used Akaike's information criterion (AIC), the χ^2 value minus twice the df (Akaike 1987). The model with the lowest value of AIC reflects the best balance of goodness of fit and parsimony. The final step in our analysis was to estimate, from the best-fitting model, and, for each of the diseases, the proportions of variance due to shared and nonshared genetic and environmental effects.

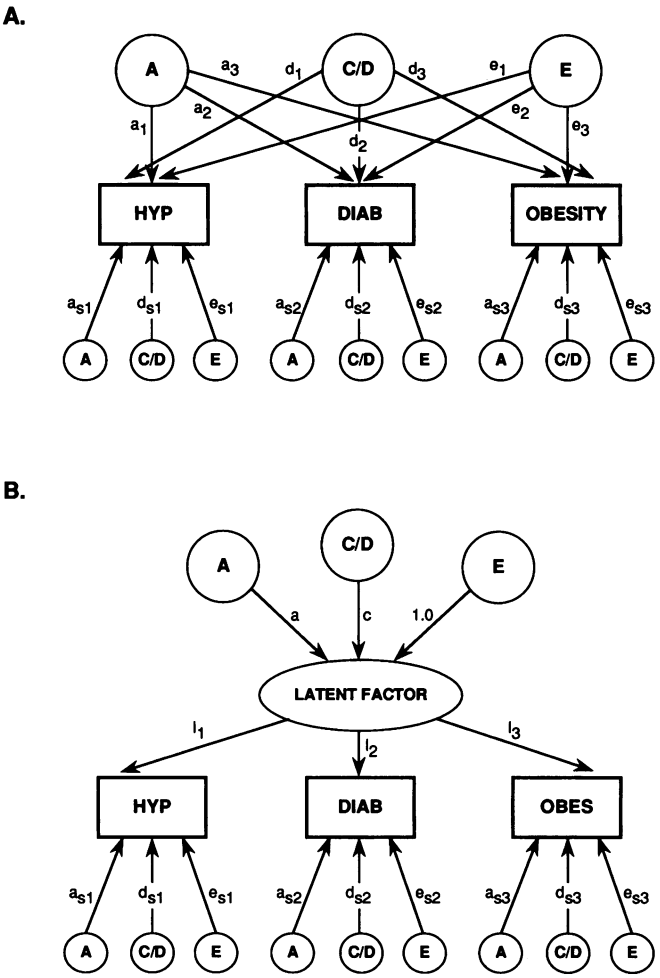

Figure 1 Path diagrams of independent-pathway model (*top*) and common-pathway model (*bottom*) of hypertension (HYP), diabetes (DIAB), and obesity (OBES). The diagrams are drawn for the case of additive genetic influences (A), dominance influences (D), shared environmental influences (C), and nonshared environmental influences (E). Parameters to be estimated are presented next to the relevant paths. In the common-pathway model, one path coefficient on the latent factor must be fixed at a constant for model identification. The diagram shows a value of 1.0 for nonshared environmental effects to satisfy this requirement. This constraint does not affect estimated parameter values or tests of significance when the estimates are standardized after WLS minimization (Neale and Cardon 1992).

Results

Prevalence, Proband Concordance Rates, and Tetrachoric Correlations

The prevalence of hypertension in the entire cohort was 34%, that of diabetes was 7%, and 16% of subjects were obese (BMI>27 kg/m^2). The joint prevalences of these conditions were as follows: hypertension and obesity, 8.5%; hypertension and diabetes, 4.1%; and diabetes and obesity, 2.5%. All three conditions were present in 70 individual subjects, or 1.4% of all the twin subjects.

The actual number of concordant affected pairs and discordant pairs, as well as the corresponding derived prevalences and probandwise concordance rates in MZ and DZ twins for each separate condition and for their joint occurrences, are shown in table 1. Prevalences did not differ significantly in MZ versus DZ twins, and concordance

Table 1

Prevalences and Concordance Rates for Hypertension, Diabetes, and Obesity among Male MZ and DZ Twins

	Total No. of Affected Individuals	*N* Pairs, Both Affected (*C*)	*N* Pairs, One Affected (*D*)	Prevalence (2*C*+*D*)/2*N*	Proband Concordance 2*C*/(2*C*+*D*)	Pairwise Concordance *C*/(*C*+*D*)
MZ twins (*N* = 1,272 pairs):						
Hypertension	899	264	371	35.3	58.7	41.6
Diabetes	189	43	103	7.4	45.5	29.5
Obesity	412	109	194	16.2	52.9	36.0
Hypertension-Diabetes	106	18	70	4.2	34.0	25.7
Hypertension-Obesity	199	31	137	7.8	31.2	22.6
Diabetes-Obesity	55	9	37	2.2	32.7	24.3
Hypertension-Diabetes-Obesity	38	6	26	1.5	31.6	23.1
DZ twins (*N* = 1,236 pairs):						
Hypertension	806	186	434	32.6	46.2	30.0
Diabetes	167	5	157	6.8	6.0	3.1
Obesity	383	54	275	15.5	28.2	16.4
Hypertension-Diabetes	99	4	91	4.0	8.1	4.2
Hypertension-Obesity	228	17	194	9.2	14.9	8.1
Diabetes-Obesity	72	1	70	2.9	2.8	1.4
Hypertension-Diabetes-Obesity	32	1	30	1.3	6.3	3.2

rates in MZ twins are consistently higher than those in DZ twins, for all the individual and joint diseases. Comparing the proportion of concordant MZ with the proportion of concordant DZ pairs, we found relative risks (RR) of 4.2, 2.1, and 11.2 ($\chi^2(1) = 4.7$, 3.9, and 4.3 [all values significant at $P<.05$]), showing a higher MZ probandwise concordance rate than DZ concordance rate, for hypertension and diabetes, hypertension and obesity, and diabetes and obesity, respectively. The probandwise concordance rate for the prevalence of all three conditions was 31.6% in MZ pairs and 6.3% in DZ pairs (RR=5.0; $\chi^2(1)=2.6$; $P<.15$).

Table 2 shows corresponding tetrachoric correlations in liabilities for MZ twins (below diagonal) and DZ twins (above diagonal). Inspection of the correlation matrices reveals that within individuals the liability to any one of these clinical conditions (underlined data in table 2) is associated with the liability to the other condition; hence, the concept of a genetic or familial commonality is supported by these data. For each separate condition—hypertension, diabetes, and obesity—we observe that MZ correlations (.55, .72, and .64, respectively) are higher than DZ correlations (.26, .08, and .33, respectively). Similarly, the cross-twin correlations for pairwise combinations of these disorders in the MZ twins are generally higher than those in DZ twins (off-diagonal boldface data in table 2).

Multivariate Model Fitting

For the correlation matrices given in table 2, we tested the goodness of fit of two multivariate genetic models: the independent-pathway model and the common-pathway model. Model-fitting statistics and significance tests of parameter estimates for these models are presented in table 3. For both models, we first established that the ADE model fits the data better than does the ACE model. Corresponding goodness-of-fit statistics were $\chi^2 = 14.29$, df = 18, and $P = .71$ for the ADE independent-pathway model, compared with $\chi^2 = 22.41$, df = 18, and $P = .21$ for the ACE independent-pathway model, and $\chi^2 = 16.31$, df = 22, and $P = .80$ for the ADE common-pathway model, compared with $\chi^2 = 24.68$, df = 22, and $P = .31$ for the ACE common-pathway model. While ACE and ADE hypotheses, embedded in either the common- or independent-pathway model, cannot be directly tested against one another, because of the confounding of shared environmental and dominance effects with twin data, the AIC statistics (table 3) suggest the presence of dominance effects rather than shared environmental influences in the present data. In addition, the pattern of observed cross-correlations in table 2, with most of the MZ cross-correlations being greater than twice the DZ cross-correlations, strongly supports this conclusion. Further, all of the C parameters can be dropped from the ACE models with no significant change in χ^2 (given as "omnibus tests" in table 3).

The goodness-of-fit and parsimony statistics indicate, however, that both the independent- and common-pathway ADE models fit the observed data ($P=.70$ and $P=.80$, respectively). The common-pathway model is the preferable model from the point of view of parsimony. Using the AIC statistic, we have AIC = −27.69 for the common-pathway model and AIC = −21.71 for the independent-pathway model. Since the largest negative value was associated with the ADE model, we adopted this model as providing the best explanation of the data. Specific tests of the

Table 2

Correlations for MZ (below Diagonal) and DZ (above Diagonal) Twins, for Hypertension, Diabetes, and Obesity

	Twin 1			Twin 2		
	Hypertension	Diabetes	Obesity	Hypertension	Diabetes	Obesity
Twin 1:						
Hypertension		.21	.27	**.26**	**.08**	**.02**
Diabetes	.30		.09	**.03**	**.08**	**.01**
Obesity	.19	.14		**.01**	**.06**	**.33**
Twin 2:						
Hypertension	**.55**	**.15**	**.05**		.24	.17
Diabetes	**.20**	**.72**	**.05**	.25		.15
Obesity	**.15**	**.17**	**.64**	.17	.11	

NOTE.—Underlined numbers indicate correlation across traits, and boldface numbers indicate correlation within twin pairs.

parameters in this model yielded a DE common-pathway model, plus additional specific genetic and environmental effects, as most parsimonious (lower portion of table 3). The parameter estimates for this model are given in figure 2.

Examination of the two common-factor loadings in figure 2 shows comparable contributions of genetic and environmental influences: .77 and .64, respectively. In addition to the shared genetic variance derived from the common factor, there was evidence for unique additive

Table 3

Tests of Significance and Goodness-of-Fit Statistics for Alternative Models of Hypertension, Diabetes, and Obesity

Model	χ^2	df	*P*	AIC	vs.	$\Delta\chi^2$	df	*P*
Alternative models: omnibus significance tests:[a]								
A. Independent:								
Pathway ACE	22.41	18	.27	−13.59				
AE	21.68	21	.42	−20.32	A	.27	3	ns
CE	499.95	21	.00	457.95	A	477.54	3	.0001
B. Independent:								
Pathway ADE	14.29	18	.70	−21.71				
DE	46.24	21	.00	4.24	B	31.95	3	.0001
C. Common:								
Pathway ACE	24.68	22	.31	−19.32				
AE	24.77	23	.36	−21.32	C	.09	1	ns
CE	555.36	26	.00	503.36	C	530.68	4	.0001
D. Common:								
Pathway ADE	16.31	22	.80	−27.69				
DE	47.83	25	.01	−2.17	D	31.52	3	.0001
Specific tests of parameter estimates in ADE common-pathway model:								
1. Drop common A	16.53	23	.83	−29.47	D	.22	1	ns
2. Drop common D	17.89	23	.76	−28.11	D	1.58	1	ns
3. Drop common A and D	49.47	24	.002	1.47	D	33.16	2	.001
4. Drop common A and specific A	47.83	25	.01	−2.17	1	31.30	3	.001
5. Drop common A and specific D	22.41	26	.50	29.59	1	5.88	1	.01

NOTE.—A, D, C, and E refer to additive genetic, dominance, shared environmental, and nonshared environmental influences respectively. $\Delta\chi^2$ represents a likelihood-ratio test of the difference between two goodness-of-fit χ^2 values, which is itself distributed as χ^2. Model parsimony and goodness of fit are summarized in the AIC (= χ^2−2df), with lower values reflecting greater parsimony and fit. ns = not significant.

[a] Omnibus tests represent omission of all model parameters for the relevant covariance component. In all full ACE models, parameter estimates of trait-specific shared environmental influences became fixed at the lower bound of 0.0. In all full ADE models, trait-specific dominance influences became fixed at 0.0 for hypertension and obesity, as did the trait-specific additive genetic parameter for diabetes. Accordingly, the df have been adjusted by 3 in all models.

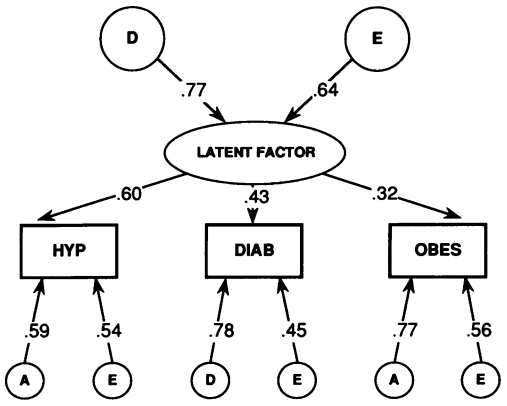

Figure 2 Best-fitting, most parsimonious common-pathway model for the causes of correlation in liabilities to hypertension (HYP), diabetes (DIAB), and obesity (OBES). Etiologic factors are divided into additive genetic effects (A), dominance genetic effects (D), and individual-specific environmental effects (E). Circles indicate the latent variables, and numbers attached to the paths are the estimated path coefficients derived from the best-fitting model. The proportions of genetic and environmental variance in liabilities are calculated from these numbers. In application to the NAS-NRC twin data, this model yields a goodness-of-fit χ^2 of 16.53 for 23 df (P=.832).

genetic variance in hypertension and obesity and for unique dominance genetic variance in diabetes. Nonshared environmental effects, specific to hypertension, diabetes, and obesity, in addition to those contributed by the common latent factor, were the major source of environmental variance.

Proportions of phenotypic variance due to A, D, and E effects (from both common and specific factors) were calculated from parameter estimates in figure 2 and are presented in table 4. The latent factor shows a broad heritability of 59%, all of which is due to dominant genetic effects. This factor is contributing to dominance genetic variance in the liability to develop hypertension (21%), diabetes (11%), and obesity (6%). Specific additive genetic variance effects, however, are the main source of genetic variance in obesity (59%) and hypertension (35%). Also, in diabetes, most of the genetic variance is specific (61%) and due to dominant genetic effects. Estimated broad heritabilities for obesity, diabetes, and hypertension were 65%, 72%, and 56%, respectively. Nonshared individual environmental effects accounted for the remaining proportions of the phenotypic variance. The contributions of the common latent factor to the environmental components of variance in hypertension, diabetes, and obesity were 15%, 8%, and 4%, respectively (table 4).

Discussion

This study represents, to our knowledge, the first application of multivariate genetic modeling techniques to the study of the clustering of cardiovascular risk factors in a large cohort of adult male twins. Using epidemiologic data from 2,508 adult male twin pairs ascertained from a population-based registry, we investigated the contribution of genetic and environmental factors to the clustering of obesity, hypertension, and diabetes in this elderly male sample.

Three major results are noteworthy. First, the greater concordance for the joint prevalence of these conditions within MZ twins compared with DZ twins suggests the presence of an underlying *common* genetic factor. The best-fitting genetic model identified a common latent factor, influenced both by genes (59%) and by the environment (41%). Second, we found that *specific* genetic and environmental effects contributed significantly to the liability to develop the individual diseases that constitute this metabolic syndrome. These effects do not overlap and have independent genetic and environmental contributions to the liability to develop hypertension, diabetes, or obesity. Third, both the pattern of cross-twin correlations for the joint prevalences of these diseases and the results of genetic model fitting suggest that all the environmental effects were of the nonshared environmental type, which tends to make twin brothers dissimilar rather than similar. Specifically, the final model estimated broad heritabilities of 56%, 65%, and 72% for hypertension, obesity, and diabetes, respectively, with the remaining 28%–44% of the variance attributed to environmental experiences that are not shared by members of a twin pair. The common genetic component accounted for 21% of total variance in hypertension, 11% of total variance in diabetes, and 6% of total variance in obesity. All the shared genetic variance was due to dominant genetic effects.

These results need to be interpreted in the context of the following potential methodological limitations. First, this study sample of World War II veterans is unlikely to be completely representative of the U.S. population. Twins who did not serve in the armed forces or were excluded from service because of medical reasons are not included in the present cohort. Second, our criteria for the assess-

Table 4

Estimated Variance Components from Best Common-Pathway Model

Variable	Additive Genetic Variance	Dominant Genetic Variance	Nonshared Environmental Variance
Hypertension	35%	21%	44% (15%)
Diabetes	...	72% (11%)	28% (8%)
Obesity	59%	6%	35% (4%)
Common factor	...	59%	41%

NOTE.—Values in parentheses represent the proportion of total variance attributable to the underlying common factor; e.g., 11% of the variance in diabetes is explained by dominance genetic effects also influencing hypertension and obesity.

ment of hypertension and diabetes were, for the majority of cases, based on subjects' self-reports, and the reliability of such assessments is far from perfect. In our model, error of measurement in twin pairs is indistinguishable from individual environmental effects (Martin et al. 1978). Had we corrected for such measurement errors, we might have been able to derive more precise estimates of genetic and environmental variance—with no change, however, in the overall conclusion regarding the presence of a significant mediating genetic component underlying the clustering of these conditions.

The present study confirms previous findings regarding the significant hereditary effects in hypertension, diabetes, and obesity. It goes beyond these findings, however, by demonstrating that a common source of genetic variance underlies the clustering of these conditions among related individuals. The identity of the latent factor involved in the clustering of hypertension, diabetes, and obesity in this cohort cannot be identified from the available data. A number of epidemiologic and laboratory studies demonstrated an association between either fasting or postglucose hyperinsulinemia and essential hypertension (Laasko et al. 1989). This characteristic is not unique to hypertension but is also found in obesity, glucose intolerance, and milder forms of diabetes and hypertriglyceridemia (Natali et al. 1991). Hyperinsulinemia typically evolves as a compensatory response to a reduced action of the hormone on target tissues (i.e., insulin sensitivity or insulin resistance). Obesity and diabetes are known conditions of insulin resistance; if coexistent with hypertension, they mark a further impairment in the ability of insulin to stimulate whole-body glucose utilization (Ferrannini and Natali 1991; Frayn and Coppack 1992).

There is now abundant evidence that the tendency to develop insulin resistance is inherited. Several studies have shown that offspring of diabetics who have normal glucose tolerance are insulin resistant compared with subjects who have no diabetic relatives (Lillioja 1987). It is therefore possible that different genes code for hypertension, diabetes, and obesity but that these genes are distributed in close and interrelated loci together with the genes of insulin resistance (linkage disequilibrium). In addition, behavioral factors are known to play a major role in the expression of insulin resistance. Diet, weight loss, and physical activity have been shown to result in improvements in insulin sensitivity (Laws and Reaven 1991).

In summary, findings from the present analysis have two important corollaries. One is that multiple abnormalities of hemodynamics and metabolism can be present at the preclinical stage of any of these diseases, thereby predicting or actually causing their development and manifestation. The other is that, as the genes are expressed, given the appropriate environmental conditions, the very existence of linked functions may feed back on other close genes, hasten their expression, and contribute to the surfacing of the whole constellation of the syndrome. Clearly, additional studies on the joint clustering of cardiovascular risk factors among related individuals are needed to assess the value of these hypotheses. These studies coupled to molecular studies should further our understanding of the interaction between environmental factors, genetic predisposition, and atherosclerotic disease.

Acknowledgments

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